EDITORIAL

Regulation of advanced therapy medicinal products will affect the practice of haematopoietic SCT in the near future: a perspective from the EBMT cell-processing committee

Bone Marrow Transplantation (2015) 50, 321–323; doi:10.1038/bmt.2014.271; published online 15 December 2014

Over the last half century, haematopoietic SCT (HSCT) emerged to become a valid therapeutic option for thousands of patients afflicted with poor-risk malignancies or inherited disorders.¹ The Nobel prize for medicine awarded to ED Thomas in 1990 recognized this achievement. Predictions that HSCT would rapidly disappear and be replaced by more modern forms of therapies including targeted therapies and personalized medicine have not been confirmed; in fact, figures are increasing as new transplant centres emerge across the world. Together with national and continental professional societies, registries such as European Society for Blood and Marrow Transplantation or Center for International Blood & Marrow Transplant Research had a key role in refining the definition of HSCT indications over time^{2,3} and in propagating initiatives for harmonization across transplant centres worldwide.⁴ A specific feature of HSCT is that it harbours 'deviations' from traditional concepts of medical care and drug delivery: the therapeutic product is made from human living cells, is produced and delivered by local, hospital-based or blood-bank-based facilities rather than by pharmaceutical companies and is administered following a conditioning regimen that includes the delivery of non-conventional doses of cytotoxic and immune-suppressive agents to the recipient. The tailored production of a haematopoietic graft for a defined recipient can be seen as an illustrative example of personalized medicine. However, the current organization of HSCT does not fit with the widely accepted schema for the production and administration of pharmaceuticals, as overseen and regulated by competent authorities. This is due to inter-individual variability in primary human haematopoietic cell collections from donors or patients, as well as to variability in technical procedures implemented by large numbers of cell-therapy facilities all of which work on a relatively small scale and produce single-recipient products.

HSCT is a rapidly evolving field in which improved knowledge of biological phenomena quickly translates into changes of medical practices. Autologous HSCT is now understood as supportive care that shares similarities with blood transfusion, whilst being differently regulated as a 'transplant product'. It is used to correct iatrogenic damage to the haematopoietic system induced by administration of high-dose chemotherapy, mostly in the context of oncohaematology. However, advances in delivery of gene therapy through stable integration of single genes into autologous HSC, as has been achieved in some congenital immune deficiencies, will increasingly see autologous HSCT becoming a regenerative medicine in its own right.

Allogeneic HSCT is used both as a form of regenerative medicine, replacing, repairing or enhancing the activity of one or several haematopoietic lineages that are affected by inherited or acquired non-malignant disorders, and as a form of anti-tumour immune therapy for recipients affected with neoplastic diseases. Allogeneic 'BMT'—as originally designed and used—has grown into a highly versatile procedure, in which different categories of donors, related

or unrelated, fully or partially HLA-matched, can be solicited to undergo various types of collection procedures that yield different cell sources. Establishment of haematopoietic chimerism follows homing and seeding of donor haematopoietic stem cells in recipient marrow niches; although chimerism is critical for the outcome of the procedure, it may not be enough to ensure full therapeutic success. Post-transplant cellular therapies of infections that develop in immune-compromised recipients and of potential or actual tumour relapses are increasingly recognized as essential components of HSCT (Figure 1). Such changes in the way we think of HSCT support the development of innovative cell-based therapeutic products, in which cells to be administered to the recipients will be more accurately defined, characterized and empowered with new functions when necessary, as opposed to the minimally manipulated cell products that are commonly used nowadays.

Along with scientific and biotechnological progress, regulations are evolving. Since 2001, cell therapies have been included in the definition of medicinal products in Europe. In 2007, the advanced therapy medicinal product (ATMP) regulation was published by the European Parliament and the Council of Europe;⁵ it will significantly affect our organization for patient care and clinical research, as it paves the way for industry to enter the field of cell-based therapies. It has already induced a shift in the balance between academia and industry for the development of these medicinal products. Until recently, academic cell-therapy facilities associated with clinical programmes saw themselves as the sole providers of cell products with therapeutic value for patients; justifiably, they tried to improve their procedures, professional practices, services and products by contributing to biomedical research, mostly without a view to license or place a product on the market.

The introduction of a new set of rules that delineate two categories of cell-based therapeutic products considering the degree/complexity of cell engineering or the function of the source material ('non-homologous use') creates challenges to academic facilities supporting conventional HSCT. These rules impose new standards in most European member states for laboratories that produce substantially manipulated products or those intended for non-homologous use in their requirement for full compliance with good manufacturing practices (GMPs).

The ATMP regulation challenges our historical organizational chart, and will have significant consequences on development, validation and clinical use of innovative cell-based therapies such as anti-viral or anti-tumour immune effectors.⁶ Currently, most cell products administered in the context of autologous or allogeneic HSCT remain classified as 'non-ATMPs', as the Committee for Advanced Therapy (CAT) of the European Medicines Agency (EMA) considers that they undergo minimal cell processing that does not substantially modify cell functions and properties. Non-substantial manipulation includes positive or negative immunoselection of target cells based on antigen recognition through a specific antibody. However, the CAT recently determined that 'occurring allogeneic donor lymphocytes (derived from a leukapheresis, BM or a whole-blood product) that are enriched for antigen-specific CD4+ and CD8+ T cells using the cytokine capture system (IFN-gamma)' are a somatic cell therapy medicinal product⁷

Figure 1. An illustration of current and future practices in allogeneic haematopoietic SCT (HSCT). Following conditioning with cytotoxic and immune-suppressive therapies, the recipient is infused with a minimally manipulated allogeneic haematopoietic cell product obtained from the selected donor; this allows for the establishment of partial or total haematopoietic chimerism. To enhance cell recovery, an expanded stem cell graft may be added or substituted to the standard minimally manipulated cell graft. In weeks following allogeneic HSCT, specific or multispecific donor-derived immune effectors may be infused to the recipient on one or several occasions, to compensate for the delayed immune recovery. For patients at high risk of tumour relapse or who actually relapsed, blood mononuclear cells obtained from the same donor may be infused again on one or several occasions (DLI). Therapeutic products that appear in red above the timeline currently qualify as cellular therapy products (CTPs) are being delivered by cell therapy/cell-processing facilities associated with each transplant programme. Therapeutic products that appear in green below the timeline currently qualify as advanced therapy medicinal products (ATMPs) in Europe, and must be manufactured and distributed in conditions compliant with European Regulation (EC) 1394/2007; ultimately, some of these therapeutic products may be manufactured and distributed by pharmaceutical companies. Other examples of post-transplant therapeutic products that qualify as ATMPs include mesenchymal stromal cells used to treat GVHD, or defined populations of *ex vivo* activated immune cells with anti-tumour activity (potential substitutes to 'crude' DLI).

despite using the same direct immunoselection process. Numerous cell therapies that are currently in development or evaluated in clinical trials with potential applications in the context of HSCT will undoubtedly qualify as ATMPs: examples are *ex vivo* expanded cord blood progenitors,^{8–11} mesenchymal stromal cells^{12,13} and various populations of cellular immune effectors with anti-tumour^{14–16} or anti-infectious activities.¹⁷ It has become imperative for clinical investigators to obtain regulatory classification of new cell therapies at the outset to determine the licensing required for manufacture.

Although the ATMP regulation was intended to fill a regulatory gap for emerging new products obtained through tissue engineering, and although major applications were seen in regenerative medicine, it is already inducing 'collateral consequences' in other fields including HSCT. Since the publication of regulation no. 2007–1394 only four ATMPs received marketing authorization from EMA, none of them with indications related to HSCT. A shared characteristic for these few ATMPs is their high price tag. Whether the introduction of innovative somatic cell products or gene therapy products, classified as ATMPs, as substitutes or additions to minimally manipulated cell products will significantly increase the overall costs of HSCT will need close monitoring. Similarly, patient access to these treatments will deserve further evaluation in the middle-to-long term. In the short term, the development of innovative post-transplant cellular therapies and their evaluation in the context of clinical trials are more difficult and expensive with the implementation of this new set of rules.

To remain at the forefront of biomedical research, academic cell-therapy facilities need to invest in new or renovated infrastructures and recruit additional personnel to fulfil the requirements of GMP. Following the development phase, some ATMPs that can be successfully commercialised will be manufactured and marketed by commercial companies, whereas other ATMPs that are unable to achieve the standards for Marketing Authorisation but are of clinical value will remain produced in academic/hospital GMP facilities.

Moving forward, hospital systems established to facilitate the interactions of three actors: 'clinical', 'collection' and 'processing' will be profoundly affected by the mode of distribution of ATMPs that in certain cases will be distributed directly from an industrial

third party to the clinical part of the HSCT programme, or through the hospital pharmacy and yet will still require the collection facility of the clinical centre and often also the storage capacity of the processing laboratory. The new biopharma companies trying to work at this logistical complexity will need to form partnerships with established clinical centres to procure, deliver and assess the performance of their ATMPs. Joint Accreditation Committee for ISCT & EBMT-accredited centres are well positioned to enter these partnerships; the Foundation for the Accreditation of Cell Therapy-Joint Accreditation Committee for ISCT & EBMT standards already recognize non-HSCT cell therapies and will continue to evolve with the field.

Following a public consultation on the ATMPs regulation, and its application in member states, the European Commission published a report on the responses and on points to consider for changes to the regulation.¹⁸ A proportion of responders stressed the lack of harmonization in the classification of ATMPs for clinical trials and in the implementation of the hospital exemption clause, as well as impact on clinical research. Possible amendments to the current regulation will depend upon the continuous active participation of stakeholders, including clinicians, scientists and academic manufacturers in this political discourse. The regulation is there to stay! Our community needs to adapt its practices to this new legal environment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We wish to express our appreciation to our many colleagues with whom we shared and discussed opinions, within EBMT, particularly JACIE, the Accreditation Committee and the former ISCT Europe Legal and Regulatory Affairs Committee.

C Chabannon^{1,2,3,4}, M Hildebrandt^{1,5}, S Scheding^{1,6}, A Humpe^{1,7}, M Lowdell^{1,8} and I Slaper-Cortenbach^{1,9}

¹Cell Processing Committee, EBMT, Barcelona, Spain;

²Centre de Thérapie Cellulaire, Institut Paoli-Calmettes, Marseille, France;

³Aix-Marseille Université (AMU), Marseille, France;

⁴Inserm CBT-1409, Centre d'Investigations Cliniques en Biothérapies, Marseille, France;

⁵Faculty of Medicine, TUMCells Interdisciplinary Center for Cellular Therapies, Technical University Munich, Munich, Germany;

⁶Hematology & Stem Cell Center, Lund University Hospital, Lund, Sweden;

⁷Division of Stem Cell and Immunotherapy, University Hospital Schleswig-Holstein Campus, Kiel, Germany;

⁸Department of Haematology, Royal Free Hospital and University College London, London, UK and

⁹Cell Therapy Facility, Department of Clinical Pharmacy, University Medical Center, Utrecht, The Netherlands

E-mail: chabannonc@ipc.unicancer.fr

or christian.chabannon@univ-amu.fr or thercell@ipc.unicancer.fr

This manuscript is based in part on a presentation made at the 2014 EBMT Annual Meeting held in Milan, 30 March–2 April.

REFERENCES

- Appelbaum FR. Hematopoietic-cell transplantation at 50. *N Engl J Med* 2007; **357**: 1472–1475.
- Passweg JR, Baldomero H, Gratwohl A, Bregni M, Cesaro S, Dreger P *et al*. The EBMT activity survey: 1990–2010. *Bone Marrow Transplant* 2012; **47**: 906–923.
- Ljungman P, Bregni M, Brune M, Cornelissen J, de Witte T, Dini G *et al*. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. *Bone Marrow Transplant* 2010; **45**: 219–234.
- Gratwohl A, Brand R, Niederwieser D, Baldomero H, Chabannon C, Cornelissen J *et al*. Introduction of a quality management system and outcome after hematopoietic stem-cell transplantation. *J Clin Oncol* 2011; **29**: 1980–1986.
- European Commission Regulation (EC) No 1394/2007 of The European Parliament and of The Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>).
- Pearce KF, Hildebrandt M, Greinix H, Scheduling S, Koehl U, Worel N *et al*. Regulation of advanced therapy medicinal products in Europe and the role of academia. *Cytotherapy* 2013; **16**: 289–297.
- European Medicines Agency Scientific recommendation on classification of advanced therapy medicinal products. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143582.pdf 2013.
- de Lima M, McMannis J, Gee A, Komanduri K, Couriel D, Andersson BS *et al*. Transplantation of ex vivo expanded cord blood cells using the copper chelator tetraethylenepentamine: a phase I/II clinical trial. *Bone Marrow Transplant* 2008; **41**: 771–778.
- de Lima M, McNiece I, Robinson SN, Munsell M, Eapen M, Horowitz M *et al*. Cord-blood engraftment with ex vivo mesenchymal-cell coculture. *N Engl J Med* 2012; **367**: 2305–2315.
- Delaney C, Heimfeld S, Brashem-Stein C, Voorhies H, Manger RL, Bernstein ID. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. *Nat Med* 2010; **16**: 232–236.
- Reiffers J, Cailliot C, Dazey B, Attal M, Caraux J, Boiron JM. Abrogation of post-myeloablative chemotherapy neutropenia by ex-vivo expanded autologous CD34-positive cells. *Lancet* 1999; **354**: 1092–1093.
- Ball LM, Bernardo ME, Roelofs H, van Tol MJ, Contoli B, Zwaginga JJ *et al*. Multiple infusions of mesenchymal stromal cells induce sustained remission in children with steroid-refractory, grade III-IV acute graft-versus-host disease. *Br J Haematol* 2013; **163**: 501–509.
- Le Blanc K, Frasson F, Ball L, Locatelli F, Roelofs H, Lewis I *et al*. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet* 2008; **371**: 1579–1586.
- Cruz CR, Micklethwaite KP, Savoldo B, Ramos CA, Lam S, Ku S *et al*. Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study. *Blood* 2013; **122**: 2965–2973.
- Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K *et al*. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med* 2014; **6**: 224ra225.
- Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A *et al*. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci Transl Med* 2011; **3**: 95ra73.
- Feuchtinger T, Opher K, Bethge WA, Topp MS, Schuster FR, Weissinger EM *et al*. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. *Blood* 2010; **116**: 4360–4367.
- European Commission Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (http://ec.europa.eu/health/files/advtherapies/2014_atmp/atmp_en.pdf 2014).